

REMARKSI. Introduction

In response to the Office Action dated May 13, 2003, new claim 25 has been added. New claim 25 differs from claim 19 by using the terms "consisting essentially of" as well as language which emphasizes the selection of buffering molecules that do not contain a free amine group. Claims 19-25 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Non-Art Rejections

On page (2) of the Office Action, claims 19-24 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner's rejection arises from the Applicants amendment to claim 19 where the terms "a buffering molecule that does not contain a free amine group and which counteracts carbon dioxide" were changed to "a buffering molecule that does not contain a free amine group and which mitigates the change in pH that results from the formation of carbonic acid". The Examiner asserts that because passages in Applicants specification (e.g. page 5, lines 18-27) "make[s] reference to CO₂ *per se*, rather than the acid which results from hydration of CO₂", the specification lacks support for the amended language in claim 19. The Examiner specifically states that because this language is not "explicitly supported" by Applicants' specification, the specification does not provide a written description of this subject matter.

Applicants respectfully traverse this rejection. While Applicants' specification may not provide an "*ipsis verbis*" description of the carbonic acid molecules which result from the hydration of CO₂ this inherent property of CO₂ in aqueous solutions is well known to those skilled in this art. Specifically, Applicants specification teaches methods of using mixed buffer systems to enhance the stability of polypeptides in aqueous solutions containing TRIS and buffering molecules that mitigate the effects of CO₂ on pH (see, e.g. page 2, lines 13-21 and page 3, lines 20-24). As is well known in the art, CO₂ in aqueous solutions inherently interacts with water molecules (i.e. "hydrates") to form carbonic acid. For example, basic instructional materials in this art teach that aqueous carbon dioxide solutions exhibit the equilibrium: CO₂ + H₂O ⇌ H₂CO₃ ⇌ H⁺ + HCO₃⁻ and that

"carbonic acid is an aqueous solution of carbon dioxide" (see, e.g. the printout from Bryn Mawr University's Chemistry 104 instructional materials that is attached herein as Exhibit A).

The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession of the claimed subject matter. See, e.g. *Ralston Purina Co. v. Far-Mar-Co.*, 227 USPQ 117, 179 (Fed. Cir. 1985). In case law pertaining to chemical compounds courts state that "the claimed invention need not be set forth in *ipsis verbis* to satisfy the description requirement . . . [F]rom a standpoint of patent law, a compound and all of its properties are inseparable. They are one and the same". See, e.g. *Ex parte Yamaguchi*, 6 USPQ2d 1805, 1807 (Bd. Pat. App. & Int'l 1987).

As noted above, the specification discloses buffer systems designed to mitigate the pH effects of CO₂ in aqueous solutions. In this context, artisans are aware of the inherent properties of CO₂ in aqueous solutions, i.e. that "carbonic acid is an aqueous solution of carbon dioxide". Therefore, one skilled in the relevant art is aware that the inventors had possession of the invention recited in claim 19. Consequently, the Examiner's assertion that claim 19 fails to satisfy the requirements of 35 U.S.C. §112, first paragraph because the specification only supports CO₂ and not its inherent properties is contrary to case law. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Finally, Applicants respectfully note that they amended claim 19 in this manner to overcome the 35 U.S.C. §112, second paragraph rejection that was raised in the last Office Action (paper #10) and in doing so merely adopted the language articulated by the Examiner.

III. Prior Art Rejections

On page (3) of the Office Action, claims 19-24 were rejected under 35 U.S.C. §103 as being unpatentable over Langballe, U.S. Patent No. 6,174,856 (Langballe). Applicants respectfully traverse this rejection for the reasons articulated below.

Independent claim 19 is directed to methods of inhibiting aggregation of a polypeptide comprising combining the polypeptide with a buffer comprising tris(hydroxymethyl)aminomethane (TRIS) mixed with a buffering molecule that does not contain a free amine group and which mitigates the change in pH that results from the formation of carbonic acid; zinc; and a phenolic preservative for a time and under conditions effective to inhibit aggregation.

The Langballe reference cited by the Examiner describes aqueous insulin compositions that can be generated using a number of different buffering molecules, some of which contain a free amine group and some of which do not contain a free amine group. As noted by the Examiner, at column 5, line 64+ Langballe teaches that their aqueous insulin compositions can include multiple buffering compounds. In this context, the Examiner further notes that when one makes every single possible combination of the various buffering molecules disclosed in Langballe, included in this series of buffer combinations is an aqueous insulin composition which includes both TRIS and a buffering molecule that does not contain a free amine group. For this reason, the Examiner asserts that Langballe renders the claimed invention obvious.

Applicants respectfully traverse the Examiner's rejection. As noted in M.P.E.P. 2143.01, the prior art must suggest the desirability of the claimed invention. While Langballe discloses a number of buffering molecules that can be used to form a wide variety of compositions, this reference provides no teaching or suggestion that would motivate one to select the subset of buffering molecules disclosed therein and then combine them with TRIS in order to arrive at the methods of the claimed invention. In particular, Applicants traverse the rejection because Langballe does not teach nor suggest the desirability of methods that involve the selection of a buffering molecule that does not contain a free amine group. In fact, Langballe provides no disclosure whatsoever regarding the chemical composition of any of the buffering molecules disclosed therein. Because Langballe fails to suggest the desirability of this element in Applicants' method claims, this reference cannot render the claimed invention obvious.

Interestingly, the Langballe disclosure does teach the desirability of using certain subsets of the buffering molecules disclosed therein. In particular, Langballe teaches "[i]t has now surprisingly been found that the stability of insulin compositions can be significantly improved by formulating the compositions using a combination of a buffer such as glycylglycine (Gly-Gly) and metal ions such as Ca⁺⁺. It has in particular been found that when the sodium phosphate buffer in a traditional insulin composition is replaced with a Gly--Gly buffer in combination with calcium ions, the formation of soluble aggregates during storage at 5° C. decreased remarkably" (column 3, lines 28-36). As noted in the response to the previous office action filed on February 28, 2003, glycylglycine is a molecule which contains a free amine group. Therefore, after reading this reference as a whole (as required by M.P.E.P. 2141.02), Applicants respectfully disagree with the Examiner's assertion that their methods that utilize TRIS combined with molecules lacking a free amine group are

obvious in view of Langballe's explicit teaching to the contrary, i.e. that it is preferable to inhibit the aggregation of polypeptides using formulations that include buffering molecules having free amine groups. In fact, by directing artisans to use "a buffer selected from glycylglycine, citrate or TRIS, in particular glycylglycine" (see Langballe's abstract, emphasis added), Langballe teaches away from the claimed invention. For this reason the disclosure in Langballe cannot render the claimed invention obvious.

Because Langballe fails to suggest the desirability of the claimed invention and in fact teaches away from the specific combination of buffering molecules recited in the claims, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §103.

Thus, Applicants submit that independent claim 19 is allowable over Langballe. Further, dependent claims 20-24 are submitted to be allowable over Langballe in the same manner, because they are dependent on independent claim 19, and thus contain all the limitations of the independent claims. In addition, dependent claims 20-24 recite additional novel elements not shown by Langballe.

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IV. Conclusion

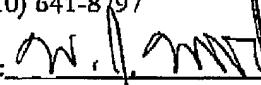
In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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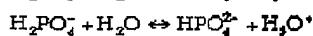
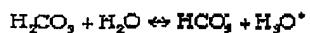
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Exhibit A

Buffer systems maintain a constant pH in blood

The body maintains the pH of blood at around 7.4. If the pH level changes just a few tenths of a pH unit, serious health consequences can result. A decrease in blood pH is called **acidosis**, an increase is called **alkalosis**.

Three different buffer systems exist in blood, the bicarbonate buffer and the phosphate buffer are composed of "simple" chemicals. In addition the carbonyl groups (-COOH) and the amide group (-NH₂) present on proteins allow some of these to act as buffers. The bicarbonate buffer and the phosphate buffer can be described by the following equilibria:



- What is the optimal pH for the bicarbonate buffer? [Answer]
- What is the optimal pH for the phosphate buffer? [Answer]
- In each buffer, which species react with added acid? [Answer]
- In each buffer, which species react with added base? [Answer]

The pH for the bicarbonate buffer seems to be outside of its ideal range

Buffer capacity is usually defined as +/- 1 pH unit of the pKa. Notice that the pH of blood is one unit away from the pKa of carbonic acid. Calculate the ratio of bicarbonate to carbonic acid implied by this. [Answer]

The ratio of bicarbonate to carbonic acid seems to be quite large (and in general this system would not be considered ideal for maintaining a pH of 7.4). However, physiologic conditions make this buffer ideal because:

- excess acid is produced by the body as a byproduct of exercise (lactic acid) making the higher concentration of the conjugate base (bicarbonate) an advantage
- the body has the ability to obtain more carbonic acid by reabsorbing carbon dioxide from the lungs. Recall that carbonic acid is an aqueous solution of carbon dioxide.

In addition, the phosphate buffer as well as the buffering ability of proteins in plasma are also available to maintain blood pH.

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